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Prevention of breast cancer

Diploma thesis

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Written Declaration

I declare that I completed the submitted work individually and only used the mentioned sources and literature. Concurrently, I give my permission for this diploma/bachelor thesis to be used for study purposes.

Prague, March 2009 Johannes Ørbeck-Nilssen

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Introduction

I selected the theme of my diploma thesis, prevention of breast cancer, based on a particular interest to the subject. Breast cancer is the second leading cause of cancer deaths among women, and the most frequent occurring cancer in the female gender. Each year more than 211,000 cases of invasive breast cancer and more than 60,000 cases of in situ breast cancer are diagnosed in the United States. Approximately 40,000 of these patients are expected to die as a result of the disease. In Norway the incidence of breast cancer in 2007 among women was 2700 cases, while the prevalence in 2007 was approximately 31500. In Denmark the incidence is estimated to be 4000 new diagnosis per year. In the Czech Republic the incidence of breast cancer in 2005 was approximately 10500 cases. The overall incidence of breast cancer has been rising because of increases in the average life span, lifestyle changes that increase risk for breast cancer, and improved survival from other diseases. However, despite an increasing incidence, mortality from breast cancer has continued to fall, thought to be the result of both earlier detection via screening and improvements in therapy. This clearly indicates the importance of exploring the opportunities of different prevention strategies. As is the case for most cancers, the cause of breast cancer is not clearly known. Also there is no cure for advanced disease, and there is no exact way to prevent it. It is vital that our knowledge and understanding of breast cancer etiology continue to grow. Identifying the risk factors decreases the probability that a person develops the disease. Another important part of prevention is to evaluate the current screening modalities, and to choose a screening strategy that provides the best results.

New medications that can reduce the risk are under development. Lifestyle changes, nutrition, use of antioxidants, exercise and weight reduction can also contribute to reducing the development of the disease. However, at current time the most important tool in improving survival of breast cancer is screening and early detection.

1. BREAST CANCER BIOLOGY AND RISK FACTORS

1.1 Genetic background

Two characteristic features define a cancer: unregulated cell growth and tissue invasion(metastasis). Cancer begins when one or more genes in a cell are mutated, creating an abnormal protein or no protein at all. The information provided by an abnormal protein is different from that of a normal protein, which can cause cells to multiply uncontrollably and become cancerous. A person may either be born with a genetic mutation in all of their cells (germline mutation) or acquire a genetic mutation in a single cell during his or her lifetime. An acquired mutation is passed on to all cells that develop from that single cell (called a somatic mutation). Somatic mutations can sometimes be caused by environmental factors. While most cancers arise sporadically, familial clustering of cancers occurs in certain families who carry a germline mutation in a cancer gene.
There are two major classes of cancer genes. The first class comprises genes that directly affect cell growth either positively(*oncogenes*) or negatively(*tumor suppressor genes*). These genes have effects on tumor growth through their ability to control cell division and apoptosis. Mutations of oncogenes may lead to uncontrolled growth. The two hit hypothesis formulated by *Knudson*, states that both alleles of tumor suppressor genes must be inactivated for cancer to occur. The second class of cancer genes, *the caretakers*, do not directly affect cell growth, but the ability of the cell to maintain its integrity of genetic material.

Research has shown that about 90-95% of breast cancers are considered sporadic, while inherited breast cancers are less common comprising 5-10% of breast cancers. Genetic mutations in certain types of genes are more likely to cause cancer. The most common gene mutations that can increase breast cancer risk occur in tumor suppressor genes(TSG). These TSG are known as breast cancer-associated genes(BRCA), BRCA1 and BRCA2. BRCA1 has been identified at the chromosomal locus 17q21; this gene encodes a zinc finger protein and the product may therefore function as a transcriptional factor. It appears to be involved in gene repair. Women who inherit a mutated allele of this gene from either parent have at least a 60-80% lifetime chance of developing breast cancer and a 33% chance of developing ovarian cancer. The risk is higher among women born after 1940, presumably due to promotional effects of hormonal factors. Men who carry a mutant allele of the gene have an increased risk of prostate and breast cancer. BRCA2 has been localized to chromosome 13q12; both men and women with this mutation have increased risk of breast cancer and other cancers(ovarian, prostatic, pancreatic and melanoma). BRCA1 and BRCA2 can now be sequenced and detected. All women with strong family history of breast cancer ahould be referred to genetic screening programs whenever possible.

The Li-Fraumeni syndrome is characterized by inherited mutations in the p53 tumor suppressor gene, which lead to an increased incidence of breast cancer, osteogenic sarcomas, and other malignancies. Other inherited mutations predisposing for the risk of breast cancer include Ataxia telangiectasia, Cowden syndrome and Peutz-Jeghers syndrome**.**

Even more important than the role these genes play in inherited forms of breast cancer may be their role in sporadic breast cancer. The p53 mutation is present in approximately 40% of human breast cancers as an acquired defect. Evidence for BRCA-1 mutation in primary breast cancer has not been reported. However, decreased expression of BRCA-1 mRNA and abnormal cellular location of the BRCA-1 protein have been found in some breast cancers. Loss of heterozygosity of some genes suggests that tumor-suppressor activity may be inactivated in sporadic cases of human breast cancer. Finally, one dominant oncogene plays a role in about a quarter of human breast cancer cases. The product of this gene, a member of the epidermal growth factor receptor superfamily, is called erbB2 (HER-2, neu) and is overexpressed in these breast cancers due to gene amplification; this overexpression can transform human breast epithelium.

Since inherited DNA defects account for only 5%-10% of breast cancers, the majority of breast cancers are due to DNA damages that develop during adult life. Environmental factors that can cause DNA damage include free radicals, chemicals, radiation, and certain toxins. Other substances such as estrogen and certain fatty acids may also increase the risk of breast cancer by stimulating the growth and division of cells of the breast tissue. Individuals without inherited cancer-causing DNA defects seem to have vulnerability to DNA damage, decreased ability to repair DNA damage, and lower ability to destroy cells with DNA damage. It seems very likely that this predisposition is genetically inherited. Even though genetically inherited predisposition accounts for a low percentage of total breast cancer cases, it is very important to identify these individuals as a part of disease prevention.**(Sabiston textbook of surgery 18th edition, Robbins basic pathology 7th edition)**

1.1 Risk factors and their evaluation

A risk factor is anything that affects your chance of getting a disease. Different cancers have different risk factors. However, risk factors tell us very little. The presence of a risk factor or several of them does not mean you will get the disease. Most women who have one or more breast cancer risk factors never develop the disease, while many women with breast cancer have no apparent risk factors (other than being a woman and ageing). Even when a woman with risk factors develops breast cancer, it is hard to know just how much these factors may have contributed to the disease. There are different kinds of risk factors. Some factors are unchangeable like a person's age or race. Others are linked to cancer-causing factors in the environment. The last important group is related to personal behaviors, such as alcohol consumption and diet. Some factors influence risk more than others, and your risk for breast cancer can change over time, due to factors such as aging or lifestyle.

The most significant risk factors for breast cancer are gender and age. Men can develop breast cancer, but women are 100 times more likely to develop breast

cancer than men. Breast cancer is 400 times more common in women who are 50 years old as compared to those who are 20 years old.

Unchangeable risk factors:

Gender: Simply being a woman can be considered the main risk factor for developing breast cancer. Even though men can develop the disease, women have many more breast cells which are constantly exposed to the growth promoting effects of estrogen and progesterone. This is believed to be main reason why women are more prone to developing cancer.
Age: The risk of developing breast cancer increases as you get older. About 1 out of 8 invasive breast cancers are found in women younger than 45, while about 2 out of 3 invasive breast cancers are found in women more than 55 years of age.
Genetics: As discussed in the previous chapter 5-10% of breast cancers are thought to be hereditary.
Family history of breast cancer: Breast cancer risk is higher among women who have a positive family history of the disease. Having one first-degree relative (mother, sister, or daughter) with breast cancer approximately doubles a woman's risk. Having 2 first-degree relatives increases the risk about 5 times. Although the exact risk is not known, women with a family history of breast cancer in a father or brother also have an increased risk of breast cancer. Altogether, about 20% to 30% of women with breast cancer have a family member with this disease. It's important to note that this means that 70% to 80% of women who get breast cancer *do not* have a family history of this disease.
Personal history of breast cancer: A woman with previous cancer in one breast has a 3-4 time higher risk of getting a new cancer in the other breast or in another part of the same breast. It is important to distinguish this from recurrence of the first cancer.
Race and ethnicity: White women are slightly more likely to develop breast cancer than are African-American women. African-American women are more likely to die of this cancer. This seems to be because African-American women tend to have more aggressive tumors, although why this is the case is not known. Asian, Hispanic, and Native-American women have a lower risk of developing and dying from breast cancer.
Benign breast conditions: *Non proliferative lesions* like fibroadenoma, phyllodes tumor, fat necrosis, mastitis, lipoma, fibrocystic disease and hyperplasia do not seem to affect breast cancer risk. *Proliferative lesions without atypia* like ductal hyperplasia, complex fibroadenoma, sclerosing adenosis, papillomas and radial scar seem to increase risk of breast cancer slightly; about 1,5-2 times.
Proliferative lesions with atypia like atypical ductal hyperplasia and atypical lobular hyperplasia increases the risk of breast cancer 4-5 times higher than normal.
Menstruation: An early menarche and late menopause appear to increase the probability slightly, probably due to prolonged exposure to estrogen and progesterone.

DES(diethylstilbestrol) exposure and previous chest radiation(especially in developing breast tissue) also predisposes to the development of the disease.

Lifestyle related risk factors:

Child bearing: Not having children or conceiving first child after age 30, increases risk of cancer.
Oral contraceptive use: Recent studies have found that women using oral contraceptive pills have a slightly greater risk of breast cancer than women who have never used them, but this risk seems to decline once their use is stopped.
Hormone replacement therapy(HRT): A study conducted by the WHI(Womens Health Initiative) have confirmed that long-term use of hormone therapy after menopause, particularly estrogens and progesterone combined, leads to an increase in risk for development of breast cancer. This risk appears to return to normal if a woman has not used hormone therapy for five years or more. The use of estrogen alone does not appear to increase the risk of developing breast cancer significantly, if at all. But when used long term (for more than 10 years), estrogen replacement therapy has been found to increase the risk of ovarian and breast cancer in some studies. At the current time there appear to be few strong indications to use post-menopausal hormone therapy, other than possibly for the short-term relief of menopausal symptoms.
Breast-feeding: Some studies suggest that breast-feeding may slightly lower breast cancer risk, especially if breast-feeding is continued for 1½ to 2 years. The explanation for this possible effect may be that breast-feeding reduces a woman's total number of lifetime menstrual cycles similar to starting menstrual periods at a later age or going through early menopause.
Alcohol: Use of alcohol is clearly linked to an increased risk of developing breast cancer. The risk increases with the amount of alcohol consumed. Compared with non-drinkers, women who consume 1 alcoholic drink a day have a very small increase in risk. Those who have 2 to 5 drinks daily have about 1½ times the risk of women who drink no alcohol. It is recommended that women limit their consumption of alcohol to no more than one drink per day.
Being overweight or obese: Being overweight or obese has been found to increase breast cancer risk, especially for women after menopause. After menopause most of a woman’s estrogen comes from fat tissue. Excessive fat tissue after menopause can increase your estrogen levels, and thereby increase your likelihood of developing breast cancer. The connection between weight and breast cancer risk is complex. The risk appears to be increased for women who gained weight as an adult but may not be increased among those who have been overweight since childhood. Also, excess fat in the waist area may affect risk more than the same amount of fat in the hips and thighs. Researchers believe that fat cells in various parts of the body have subtle differences that may explain this. It is recommended to maintain a healthy weight throughout life by balancing food intake with physical activity and avoiding excessive weight gain.

Lack of physical activity: Evidence is growing that physical activity in the form of exercise reduces breast cancer risk. In one study from the Women's Health Initiative (WHI) as little as 1.25 to 2.5 hours per week of fast walking reduced a woman's risk by 18%. Walking 10 hours a week reduced the risk a little more. To reduce your risk of breast cancer, it is recommended to perform 45 to 60 minutes of intentional physical activity 5 or more days a week.

Risk factors with uncertain, controversial or unproven effect on breast cancer risk include high-fat diets, smoking, antiperspirants, bras, induced abortion, breast implants, chemicals in environment and night work.
It is important to remember that 75% of women who develop breast cancer have no risk factors other than age. Thus, screening and early detection are important to every woman regardless of the presence of risk factors.**(Sabiston textbook of surgery 18th edition, 22,23,24,25,26,27,28,29,30, 31)**

2. SCREENING MODALITIES

2.1 Breast self-examination

The various types of cancers behave differently, with distinct rates of growth and patterns of spreading metastasis to other areas of the body. Some cancers are favorable and treatable, while others are so aggressive and malignant that almost nothing in modern medicine can help.
Compared to other cancers, breast cancer is on the more treatable end of the spectrum if diagnosed early. It is considered a "favorable" cancer because it can be detected early by breast examination or by mammography.
Studies have clearly shown that the smaller the size of the breast cancer when detected, the better the chance of a surgical cure and long term survival. The likelihood of a cure is also higher if the cancer is removed before it has spread to lymph nodes and other organs such as the lungs, liver, bones, and brain.
Currently, mammography and breast examinations serve as the foundation for screening for breast cancer. It is extremely important for a woman to have regular breast examinations as well as mammograms to detect early breast cancer.

The breast self-exam (BSE) is a way that you can check your breasts for changes (such as lumps or thickenings) that may signal breast cancer. When breast cancer is detected in its early stages, your chances for surviving the disease are greatly improved. While 80% of all breast lumps are not cancerous, you can help catch potentially serious changes in the breast early by regularly performing a self-exam. It has long been recommended that all women over the age of 20 years old should perform a monthly BSE. However, new information now suggests that doing a breast self-exam doesn't improve breast cancer survival, and it doubles the likelihood that biopsies of benign breast lumps are made. The new review is based on two studies that together included more than 388,500 women in Russia and China who ranged in age from 30-66.

Some of the women were trained to do breast self-exams. They also got regular classes to make sure their technique was correct. For comparison, the other women in the studies were not taught or told to do breast self-exams.
The women were followed for 10 years. During that time, 587 women died of breast cancer, with similar numbers of deaths in the breast self-exam group (292 breast cancer deaths) and in the group of women who weren't trained to do breast self-exams (295 breast cancer deaths).
The women who did breast self-exams were nearly twice as likely to get breast biopsies, many of which turned out not to show cancer.
In short, doing breast self-exams made no difference to the groups' breast cancer survival rates, and it boosted the biopsy rate. At the current time the general opinion about BSE among oncologists, are that they don't want to recommend against it but there is no evidence to recommend it as a part of breast cancer prevention. **(7)**

2.2 Clinical breast examination

A clinical breast examination (CBE) is a physical examination of the breast done by a health professional. Clinical breast examinations are used along with mammograms to check women for breast cancer. Clinical breast examinations are also used to check for other breast problems.
Medical experts disagree about the need for regular clinical breast examinations. Some doctors recommend regular CBE. However, the US Preventive Services Taskforce(USPST) says that studies do not show support for or against regular CBE. Some studies show that mammogram tests alone reduce breast cancer deaths just as well as using mammograms and CBE. At the current time no clinical trial has compared CBE alone with a no-screening condition, and evidence demonstrating that mammography alone reduces breast cancer mortality makes it highly unlikely that a trial of CBE alone will ever be conducted. CBE can contribute to the ability of health care professionals and women to detect some breast cancers, but there are no current proof that it alone decreases overall mortality.**(6)**

2.3 Mammography

A mammogram is an X-ray picture of the breast used to screen for breast problems, such as a lump, fluid-filled cysts or a solid mass. Mammograms are at the present time the best method to detect breast cancer early. Early discovered cancer is generally easier to treat, and gives an increased survival rate. Having regular mammograms can lower the risk of dying from breast cancer. Experts have different recommendations for how often a mammogram should be performed.
For women older than age 50, regular mammograms (every 1 to 2 years) are recommended. For women between the ages of 40 and 50, the benefits of mammogram are not as clear. Some organizations recommend mammograms

every 1 to 2 years while others recommend mammograms every year. Most organizations recommend that women have their first mammogram at age 40. The American Cancer Society(ACS) recommends a baseline mammogram for all women by age 40 and annual mammograms for women 40 and older for as long as they are in good health.
Women with "lumpy breasts" or breast symptoms, and also in women with a high risk of developing breast cancer, sometimes a baseline mammogram at 35 years of age is recommended. This kind of recommendation is somehow controversial, and there are different opinions. In young women with increased risk of breast cancer there are special considerations. Since young women have dense glandular breast tissue, routine mammograms have difficulty "seeing through" the dense breast tissue. Therefore mammograms may not be able to detect cancer in the breast because the dense breast tissue around the cancer hides it. However, this problem can be partly offset by the use of special breast ultrasound, which is used as an important additional imaging technique. It works as a valuable tool supporting mammography in difficult cases. Ultrasound can make visible a lump hidden within dense breast tissue. It may also detect lumps and early breast cancers when mammograms fail to identify a problem. About 85%-90% of breast cancers are detectable by mammography. Early detection by mammography has reduced the mortality rate from breast cancer by 20%-30% in women over 50 years of age. However, some 10%-15% of breast cancers are not visible on mammography but can be felt on physical examination of the breast. Therefore, a normal mammogram does not exclude the possibility of breast cancer. Breast examination by palpation and visual inspection is also important.
Generally there are two types of mammography. Screening and diagnostic mammography and the two should not be confused. Diagnostic mammography is aimed at evaluating the rest of the breast before biopsy is performed or as a strategy to exclude the need for biopsy. If small abnormalities are detected by screening mammography it should be evaluated by compression or magnified views. Some of these abnormalities include clustered microcalcifications, densities and enlarging or new structural distortion. Screening mammography means an examination of a group of usually asymptomatic individuals to detect those with a high probability of having a given disease.
Breast cancer is unique among epithelial tumors in that screening has been proven to improve survival. Meta-analysis examining outcomes from every randomized trial of mammography, conclusively shows a 25-30% reduction in the chance of dying from breast cancer with annual screening after 50 years of age. Concerning women between 40-50 years of age the numbers are almost as positive, but more studies are needed to draw conclusions. While controversy continues to surround the assessment of screening mammography, the current literature strongly support the positive benefits of screening mammography.**(1,2,3,4,5)**

2.4 Magnetic resonance imaging

According to new research MRI scanning may be a useful screening tool for breast cancer in certain high-risk populations. In 2004, some Dutch researchers published a study of over 1,900 women at high risk for breast cancer in the *New*

England Journal of Medicine. The women involved in this study underwent breast-cancer screening consisting of physical exams, every six months along with yearly mammograms and MRI scans of the breasts. In the study conventional mammography did detect many cancers at an early stage, but some tumors were identified by MRI that was not detected by mammography. To summarize MRI led to the identification of 32 tumors, of which 22 were not seen on the corresponding mammogram. Likewise, some tumors appeared on mammograms that were not visible on the MRI scan. Mammography detected a total of 18 tumors, of which eight were not identified by MRI.
Routine use of MRI as screening modality is widely discussed among health professionals. The reason is that it has several limitations. In several studies it detected several tumors in high risk women, but also had a certain amount of false positives. The main concern of this is unnecessary medical procedures. Some literature suggests that MRI leads to twice as many unnecessary examinations and three times as many unneeded surgical biopsies than by mammography alone. Another disadvantage of magnetic resonance imaging is the cost. One MRI examination costs ten times more than mammography. With these limitations in mind at the present time experts believe that MRI is impractical for women who do not have elevated risk of developing breast cancer. However its benefits appear to outweigh its limitations in certain high risk populations. In March 2007, the American Cancer Society Breast Cancer Advisory Group issued new breast-cancer-screening recommendations that include MRI scanning along with mammography for women aged 30-69 who are considered to have an estimated lifetime risk of developing breast cancer of 20%-25%. The latest research imply that there is insufficient evidence to support routine use of MRI as screening in women with other risk factors; including personal history of breast cancer, carcinoma in situ or atypical hyperplasia or dense breast tissue. It is important to understand that MRI should not be considered a substitute for regular mammography, but rather a contributor in screening high risk individuals. Therefore the role of MRI in breast imaging for average-risk women generally is used for diagnostic evaluation, including evaluating breast implants, assessing palpable masses following surgery or radiation therapy, and detecting cancers that are not picked up by mammography. It can also be utilized in patients with axillary nodal metastasis and preoperative planning.**(10,11,12)**

2.5 Other modalities

Ultrasonography: The most recent research recommend ultrasound in the evaluation of palpable or mammographically identified masses, or particular difficult cases. However at the current time there is little evidence that can support the routine use of a ultrasound as a screening modality.**(9)**
Scintimammography: Scintimammography, using technetium-99m sestamibi or technetium-99m tetrofosmin, scans the axilla and supraclavicular region while at the same time imaging the breast tissue. In staging women with a known breast cancer, the contralateral arm is injected with the radionuclide, and lateral and anterior projections are imaged with a gamma camera, with both arms raised. The theoretical advantage of this technology is the potential to obtain staging

information. There are currently ongoing clinical trials evaluating its use and efficacy, but at present time there is too little evidenced based material to implicating its use.(32)
Tissue sampling: Currently studied is the use of fine needle aspiration, nipple discharge and ductal lavage as screening in high risk individuals.(13)

3. BREAST CANCER PREVENTION TREATMENT

3.1 Selective estrogen receptor modulators(SERM)

Selective estrogen receptor modulators are drugs that antagonizes the effects of estrogen in breast tissue. Cells in other tissues in the body, such as bones and the uterus, also have estrogen receptors. But each estrogen receptor has a slightly different structure, depending on the kind of cell it is in. So breast cell estrogen receptors are different from bone cell estrogen receptors and both of those estrogen receptors are different from uterine estrogen receptors. Since SERMs are selective they can activate estrogen's action in other cells, such as bone, liver, and uterine cells. Two SERMs have been used as preventive treatment, namely Tamoxifen and Raloxifen.
Tamoxifen was the first SERM to be approved by FDA in United States for prevention of breast cancer. Tamoxifen blocks the action of estrogen on the cancer cells by occupying the receptors. By blocking estrogen from acting on estrogen sensitive cancer cells, Tamoxifen stops the growth and proliferation of these cells. It has also been shown that Tamoxifen cause death of non-estrogen sensitive cancer cells. It has been used both for treatment of advanced and early stage cancers. Recent studies show that it reduces the risk of developing cancer in the other breast as well. Some authors suggest that it also have a role in preventing fractures in patients with osteoporosis in postmenopausal women.
Other functions of the drug include reduction of cysts and lumps in breast tissue, making it easier to perform screening tests, especially in young women.
The use of Tamoxifen in primary prevention, by reducing the risks of developing breast cancer in women without a previous history of the disease has also been studied. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1, more than 13,000 women considered at high risk for developing breast cancer were given either tamoxifen or placebo for five years. The women receiving tamoxifen developed 49% fewer breast cancers than women receiving the placebo. A further study, the International Breast Cancer Intervention Study (IBIS-I) in Europe, also confirmed a reduction in the rate of breast-cancer development in high-risk women. In women at high risk for developing breast cancer the FDA has approved Tamoxifens use. Currently there exists no evidence that Tamoxifen can reduce cancer risk in women with normal risk.
Some of the adverse effects of the drug includes; development of uterine cancer and increased risk of deep vein thrombosis. Other more benign side effects include weight gain, hot flashes, irregular periods, vaginal dryness or discharge, and a slightly enhanced risk of catarcts. The development of adverse effects are highly individual and very dependent on age.
Raloxifen was the second SERM to be approved by FDA. It has been used in prevention of fractures in osteoporotic postmenopausal women. Recent studies

suggest that it has similar effects like Tamoxifen. However it seems to have less risk for developing uterine cancer. Studies that examined the effects of both tamoxifen and raloxifene (including the STAR trial, which studied over 19,000 postmenopausal women at high risk for developing breast cancer) showed that both drugs decreased the incidence of breast cancer in a similar manner. While both tamoxifen and raloxifene increased a woman's risk of blood clots, the increase was smaller with raloxifene. Raloxifene was also associated with a lower risk of uterine cancer. Some data suggested that raloxifene might not be as effective in preventing the development of early, noninvasive cancers as tamoxifen.
Other pharmacologic drugs, known as aromatase inhibitors, are also used to block the effects of estrogen. They act by inhibiting aromatase, an enzyme involved in synthesis of estrogen. Tamoxifen and aromatase inhibitors, therefore, act differently and have different side effects. At the current time studies are being conducted to compare their use as breast-cancer preventive drugs together and separately.
Several questions have not been answered as of yet. Whether they increase survival, if they only suppress the growth of existing breast cancer, long term adverse effects and how long people should be kept on the medication. Further studies are needed to answer these questions. Similar studies are being conducted among women with genetic predisposition; namely BRCA mutations.**(14,15,16,17,18)**

3.2 Surgical prevention

Preventive mastectomy or surgical prevention of breast cancer means the removal of one or more breasts in moderate to high risk women to prevent development of cancer. Some possible indications for preventive surgery include;
-Previous cancer
-Strong family history
-Gene mutation
-Carcinoma in situ
-Previous radiation to the chest before age 30.

Published data suggest that this method decreases the risk of getting breast cancer by 90% in high risk individuals. High risk individuals, generally refers to people with BRCA mutations. However this method is not 100%, because small amounts of breast tissue may remain on the chest wall, in axilla or even in the abdomen, after mastectomy. Other recent studies show that in these high risk women with BRCA mutation, a preventive oophorectomy may reduce the risk of breast cancer with 50%. No evidence exists for recommending preventive mastectomy in women with low cancer risk.
The adverse effects of this procedure, except for the obvious cosmetic defect, are general surgical complications like bleeding and infection. There is also a risk of iatrogenic metastasis of the cancer.
It is very important that these individuals are offered surgical reconstruction of the breast defect, either by musculocutaneous flaps or breast implants. Removal of mammary glands are associated with significant psychological detrimental effects.**(19,20,21)**

3.3 Other preventive measures

Free radicals are electrically charged chemicals that can attack and damage proteins and DNA, thereby altering genetic information. If enough damage occurs to the DNA segments of a cell that controls cell division and growth, cancer can develop from that single cell. To prevent damage by these radicals, people at risk for breast cancer are recommended to consume antioxidants.

Antioxidants: An Antioxidant is a type of chemical that prevents oxidative stress. Some antioxidants that are recommended to ingest are beta-carotene, vitamin E and vitamin C. Caffeine is a widely discussed topic because it possesses antioxidant effects, but currently there exist no evidence connecting it to breast cancer risk.

Low fat diet: Past epidemiological studies suggested that high fat diets might be associated with increased risks of breast cancer, but this relationship has not been confirmed. What has been confirmed, is that some fats are harmful, and some are protective. Some theories suggest that there exist different metabolic activity of enzymes involved in fat metabolism. One of them is lipooxygenase, which converts linoleic acid and arachidonic acid into chemicals that are potent stimulators of cell growth. These chemicals also promote the growth of cancers and increases risk of metastasis.
Protective fatty acids include Omega-3-fatty acids, which are widely found in fish.
Health professionals generally recommend people at risk of breast cancer to consume a low fat diet and avoid overcooked meats. Other dietary recommendations include vegetables and fruits. **(33,34)**

Exercise: There is epidemiological data which show that women who exercise regularly have a lower incidence of breast cancer than women who do not exercise. The reason for such a benefit is unknown, but it may be related to the fact that obese individuals are more exposed to estrogen which leads to proliferation of breast tissue.

Although these recommendations make sense and are part of an overall healthy way of living, no clear and convincing proof that they specifically reduce the risk of developing breast cancer, exist.**(Harrison principles of internal medicine 16th edition)**

CONCLUSION

When considering prevention of breast cancer it is necessary to distinguish people according to risk level. Although the common goal is prevention of breast cancer, the approach is somehow different. There are generally two essential parts of breast cancer prevention; early detection and reduction of risk factors. To date, the best way to identify early cancerous changes are the routine screening of women with a combinated approach of clinical breast examination and routine mammography in women over age 40. Detection of invasive and noninvasive cancers at an early stage, by means of screening, clearly leads to a decreased mortality rate. However, screening does not prevent breast cancer development, it prevents on a secondary level by allowing early detection and prompt treatment of the disease. In high risk individuals, there are currently two options: Bilateral prophylactic mastectomy and prophylactic SERM therapy. Mastectomy may have a role in preventing breast cancer in high risk patients, but it is associated with dramatic physical and psychological negative effects. Therefore as a second option is prophylactic use of selective estrogen receptor modulators. Tamoxifen has shown to significantly reduce the risk of breast cancer in women at high risk. The use of Tamoxifen has to be carefully evaluated with potential adverse effects in mind. Screening high risk women should start at en earlier age, from 25-35 years of age. The combinated use of clinical breast examination, mammography and MRI are currently recommended.

At the current time it is important that breast cancer prevention is really understood as risk reduction. There is no certain way to prevent breast cancer as of yet. However, all women regardless of their risk level, should be encouraged to have a healthy lifestyle. Obese and overweight individuals should be motivated to lose weight. A rigorous exercise routine should be established. A healthy diet with low fat and overcooked meat should be avoided. A reduction in alcohol intake and avoiding smoking(although no clear evidence exist connecting smoking to breast cancer), can easily be recommended.

SUMMARY

Breast cancer is the most frequent cancer and the the 2nd leading cause of cancer deaths occurring in women. Each year in the United States approximately 211,000 women are diagnosed with invasive breast cancer, and close to 60,000 are diagnosed with in situ cancer. Of these patients about 40,000 are expected to die from the disease. The etiology of breast cancer is not clearly known, but it is believed to be a combination of both genetic and environmental factors. According to research about 90-95% of breast cancers occurs sporadic, while 5-10% are believed to be inherited. The most common genetic mutations increasing the risk of cancer are BRCA1 and BRCA 2. Individuals carrying this mutation has a 60-80% lifetime risk of getting breast cancer. However, the most important risk factors associated with breast cancer are female gender and increasing age. Lifestyle related risk factors such as HRT(hormone replacement therapy), oral contraceptives, obesity, lack of exercise, alcohol consumption also contribute to an increased risk. It is important to remember that the presence or absence of risk factors does not mean you will get the disease. In fact 75% of women who get breast cancer have no other risk factors than gender and increasing age.
Currently the best preventive options for breast cancer is early detection by screening and risk reduction. Breast self-examinations have long been thought as an important tool in breast cancer screening. However at the current time there exist no evidence to recommend it as a part of breast cancer prevention. Clinical breast examination and mammography is at the present time recommended as routine screening of breast cancer in women over 40 years of age. In high risk individuals an earlier onset of screening is recommended. Generally from age 25-35 years of age, with a combinated approach of clinical breast examination, mammography and magnetic resonance imaging. The use of selective estrogen receptor modulators and prophylactic mastectomy is justified in high risk individuals as primary prevention.
Secondary prevention of breast cancer by screening and early detection is by date the most important part of decreasing the mortality rate of breast cancer patients. At the current time it is important that breast cancer prevention is really understood as risk reduction. There is no certain way to prevent breast cancer as of yet, but all women should be encouraged to adopt a healthy lifestyle, with regular exercise, limited fat and alcohol intake, and a healthy body weight. A reduction of known risk factors decreases the probability of getting the disease.

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Attachments (37,38,39)

Factors Associated with Increased Risk of Breast Cancer

Hormone replacement therapy/hormone therapy

Based on solid evidence, combination hormone replacement therapy (HRT; estrogen-progestin), also called hormone therapy (HT), is associated with an increased risk of developing breast cancer. The evidence concerning the association between estrogen-only therapy and breast cancer incidence is mixed.

Magnitude of Effect for Combination Therapy: Approximately a 24% increase in incidence of invasive breast cancer.

Study Design: Randomized controlled trials.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Magnitude of Effect for Estrogen Only: Cannot determine because of mixed evidence.

Study Design: Randomized controlled trials.
Internal Validity: Good.
Consistency: Poor.
External Validity: Not applicable.

Ionizing radiation

Based on solid evidence, exposure of the breast to ionizing radiation is associated with an increased risk of developing breast cancer, starting 10 years after exposure and persisting lifelong. Risk depends on dose and age at exposure, with the highest risk occurring during puberty.

Magnitude of Effect: Variable, but approximately a six fold increase in incidence overall.

Study Design: Cohort or case-control studies.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Obesity

Based on solid evidence, obesity is associated with an increased breast cancer risk in postmenopausal women who have not used HRT/HT. It is uncertain whether reducing weight would decrease the risk of breast cancer.

Magnitude of Effect: The Women's Health Initiative observational study of 85,917 postmenopausal women found body weight to be associated with breast cancer. Comparing women weighing more than 82.2 kg with those weighing less than 58.7 kg, the relative risk (RR) was 2.85 (95% confidence interval [CI], 1.81–4.49).

Study Design: Observational study.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Alcohol

Based on solid evidence, exposure to alcohol is associated with an increased breast cancer risk in a dose-dependent fashion. It is uncertain whether decreasing alcohol exposure would decrease the risk of breast cancer.

Magnitude of Effect: The RR for women consuming approximately four alcoholic drinks per day compared with nondrinkers is 1.32 (95% CI, 1.19–1.45). The RR increases by 7% (95% CI, 5.5%–8.7%) for each drink per day.

Study Design: Case-control and cohort studies.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Major inheritance susceptibility

Based on solid evidence, women who inherit gene mutations associated with breast cancer have an increased risk.

Magnitude of Effect: Variable, depending on gene mutation, family history, and other risk factors affecting gene expression.

Study Design: Cohort or case-control studies.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Factors Associated with Decreased Risk of Breast Cancer

Exercise

Based on solid evidence, exercising strenuously for more than 4 hours per week is associated with reduced breast cancer risk.

Magnitude of Effect: Average RR reduction is 30% to 40%. The effect may be greatest for premenopausal women of normal or low body weight.

Study Design: Prospective observational and case-control studies.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Early pregnancy

Based on solid evidence, women who have a full-term pregnancy before age 20 years have decreased breast cancer risk.

Magnitude of Effect: 50% decrease in breast cancer compared to nulliparous women or those who give birth after age 35 years.

Study Design: Cohort and case-control studies.
Internal Validity: Good.

Consistency: Good.
External Validity: Good.

Breast-feeding

Based on solid evidence, women who breast-feed have a decreased risk of breast cancer.

Magnitude of Effect: The relative risk of breast cancer is decreased 4.3% for every 12 months of breast-feeding, in addition to 7% for each birth.[1]

Study Design: Cohort and case-control studies.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Interventions Associated with Decreased Risk of Breast Cancer

Selective estrogen receptor modulators (SERMs): Benefits

Based on solid evidence for tamoxifen and fair evidence for raloxifene, treatment reduces the incidence of breast cancer in postmenopausal women. Tamoxifen also reduced the risk of breast cancer in high-risk premenopausal women. The effects observed for tamoxifen show persistence several years after discontinuing active treatment.

Magnitude of Effect: Treatment with tamoxifen reduced breast cancer by about 50%. Treatment with raloxifene has a similar effect on reduction of invasive breast cancer but appears to be less effective for prevention of noninvasive tumors.

Study Design: Randomized controlled trials.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Selective estrogen receptor modulators (SERMs): Harms

Based on solid evidence, tamoxifen treatment increases the risk of endometrial cancer, thrombotic vascular events (pulmonary embolism, stroke, deep venous thrombosis), and cataracts. Many of these risks, notably pulmonary embolism and deep venous thrombosis, are reduced after discontinuing active treatment with tamoxifen. Based on fair evidence, raloxifene also increases venous pulmonary embolism and deep venous thrombosis but not endometrial cancer.

Magnitude of Effect: Meta-analysis shows RR = 2.4 (95% CI, 1.5–4.0) for endometrial cancer and 1.9 (95% CI, 1.4–2.6) for venous thromboembolic events.

Study Design: Randomized controlled trials.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Aromatase inhibitors or inactivators: Benefits

Based on fair evidence, aromatase inhibitors or inactivators (AIs) reduce the incidence of new breast cancers in postmenopausal women who have a history of breast cancer.

Magnitude of Effect: Compared with tamoxifen treatment, treatment with anastrozole reduces the incidence of new primary breast cancers by 50%. Similar results have been reported with letrozole and exemestane treatment.

Study Design: Randomized controlled trials performed in postmenopausal women with a previous history of breast cancer.
Internal Validity: Good.
Consistency: Good.
External Validity: Fair.

Aromatase inhibitors or inactivators: Harms

Based on fair evidence, AIs are associated with decreased bone mineral density, increased falls, and decreased cognitive function.

Magnitude of Effect: Fracture rate for women being treated with anastrozole was 5.9% compared with 3.7% for those being treated with tamoxifen.[2]

Study Design: Multiple randomized controlled trials demonstrate decreased bone mineral density with each AI. One randomized controlled trial shows an increase in fractures (in those using anastrozole).
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Prophylactic mastectomy: Benefits

Based on solid evidence, bilateral prophylactic mastectomy reduces the risk of breast cancer in women with a strong family history.

Magnitude of Effect: Risk is reduced as much as 90%, but published study designs may have produced an overestimate.

Study Design: Evidence obtained from case-control and cohort studies.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Prophylactic mastectomy: Harms

Based on fair evidence, physical and psychological effects include anxiety, depression, and impaired body image.

Magnitude of Effect: 6% of women were dissatisfied with their decision to have a prophylactic mastectomy, usually for cosmesis. Regrets about mastectomy were less in 185 women who opted not to have reconstruction than in 111 women who chose it.[3]

Study Design: Convenience sample.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Prophylactic oophorectomy or ovarian ablation: Benefits

Based on solid evidence, prophylactic oophorectomies in women with *BRCA* gene mutations document lower breast cancer incidence. Similarly, oophorectomy or ovarian ablation is associated with decreased breast cancer incidence in normal women or in those who received thoracic irradiation.

Magnitude of Effect: Breast cancer incidence is decreased by 50%, but published study designs may have produced an overestimate.

Study Design: Observational, case-control, and cohort studies.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.

Prophylactic oophorectomy or ovarian ablation: Harms

Based on solid evidence, castration may cause the abrupt onset of menopausal symptoms such as hot flashes, insomnia, anxiety, and depression. Long-term effects include decreased libido, vaginal dryness, and decreased bone mineral density.

Magnitude of Effect: Nearly all women experience some sleep disturbances, mood changes, hot flashes, and bone demineralization, but the severity of these symptoms varies greatly.

Study Design: Case-control, cohort, and observational studies.
Internal Validity: Good.
Consistency: Good.
External Validity: Good.